REMARKS

Upon entry of this submission, claims 24, 28, 29, 32, 33 and 37 remain pending and stand rejected under 35 U.S.C. 103(a) as being unpatentable over Marx et al. (*Circ. Res.* **90**:703-710, 2002; hereinafter "Marx") in view of Shidoji et al., WO 01/80854, as evidenced by the English equivalent US 2005/0250671 A1 (and hereinafter collectively referred to as "Shidoji" and with reference being made to the disclosure as set forth in US 2005/0250671 A1).

Applicant submits that there is no reason to arrive at Applicant's claimed subject matter based upon any combination of Marx and Shidoji. Marx in view of Shidoji fails to teach or suggest a method wherein the activation of a transcription factor KLF5 is inhibited and/or wherein vascular remodeling is inhibited let alone a method of treatment for arteriosclerosis, comprising administering to a mammal in need of treatment a medicament comprising (2E,4E,6E,10E)-3,7,11,15-tetramethyl-2,4,6,10,14-hexadecapentaenoic acid (hereinafter also referred to as "NIK-333") as an active ingredient such that activation of a transcription factor KLF5 is inhibited and/or such that vascular remodeling is inhibited. There is no direction in either of Marx or Shidoji and/or any combination of Marx and Shidoji to arrive at a method of treatment for arteriosclerosis in a mammal in need thereof using NIK-333, to arrive at a method of administering NIK-333 to a mammal in need of treatment let alone administering NIK-333 to a mammal in need of treatment such that such that activation of a transcription factor KLF5 is inhibited and/or such that vascular remodeling is inhibited.

Still further, while even the combined disclosures of Marx and Shidoji do not teach or suggest Applicant's claimed subject matter, there is no reason why one having ordinary skill in the art would have sought to combine the disclosures of Marx and Shidoji. One having ordinary

skill in the art would not have sought to combine the teachings of Marx with those of Shidoji at least because Shidoji and Marx are directed to disparate subject matter. Marx is a research report which discloses the results of experiments performed to determine the effect of PPAR activators on CD4+ T cells. For example, the abstract of Marx, beginning in line 5, discloses:

> The present study investigated whether activators of peroxisome proliferator-activated receptor (PPAR)α and PPARγ, with their known antiinflammatory effects, might regulate the expression of proinflammatory cytokines in human CD4-positive T cells.

In contrast, Shidoji is directed to activators of peroxisome proliferator-activated receptors comprising a polyprenyl compound, preferably (2E,4E,6E,10E)-3,7,11,15-tetramethyl-2,4,6,10,14-hexadecapentaenoic acid, as an active ingredient, and medicaments for preventive and/or therapeutic treatment of hyperlipidemia, non-insulin dependent diabetes mellitus or the like comprising a polyprenyl compound as an active ingredient. Therefore, Shidoji discloses the use of PPAR activators in the treatment of hyperlipidemia and non-insulin dependent diabetes.

Thus, the disclosure of Shidoji relating to treatment of hyperlipidemia, non-insulin dependent diabetes mellitus or the like is in contrast to that of Marx directed to investigating whether activators of peroxisome proliferator-activated receptor (PPAR)α and PPARγ, with their known antiinflammatory effects, might regulate the expression of proinflammatory cytokines in human CD4-positive T cells.

Therefore, not only would one having ordinary skill in the art not have combined the cited art in the manner contended in the rejection, it would not have been obvious to treat arteriosclerosis with NIK-333 absent knowledge provided by Applicant that such a compound inhibits KLF5 and/or inhibits vascular remodeling.

In the rejection, the Examiner asserts that inhibition of vascular remodeling would be obvious because "...Marx teaches that PPAR activators (i.e. 3,7,11,15-tetramethyl-2,4,6,10,14 hexadecapentanoic acid) are useful for reducing inflammation in transplant associated arteriosclerosis." (See page 4, Section 10 of the Final Office Action). However, even if Marx discloses that PPAR activators are useful for reducing inflammation in transplant-associated arteriosclerosis, this does not mean that Marx discloses inhibition of vascular remodeling, either explicitly or inherently. Indeed, the Examiner appears to concede at page 6, section 16 of the Office Action that any reduction in the expression of proinflammatory cytokines from the activation of PPAR yields only "potential" therapeutic benefits in pathological processes such as atherosclerosis and transplantation-associated arteriosclerosis.

The Examiner appears to be asserting that one of ordinary skill in the art could envisage use of NIK-333 in the method of Marx with a reasonable expectation of success (see Office Action at page 4, section 11, and pages 6-7, section 19). However, use of NIK-333 in the method of Marx would result in pre-treatment of human CD4-positive T cells in culture with NIK-333, not administration of NIK-333 to a mammal in need of treatment for arteriosclerosis as claimed. Thus, Applicant's claimed subject matter cannot be achieved by a simple substitution of NIK-333 in the method of Marx as the Examiner appears to assert.

During an October 27, 2010 telephone interview, the Examiner contended that Marx discloses, at page 704, left column, first full paragraph, that given the role of T-lymphocyte inflammatory cytokine production in atherosclerosis and evidence of PPARs as anti-inflammatory mediators, it is hypothesized that human T lymphocytes express PPARα and PPARγ and that stimulation of these cells by PPAR activators in clinical use would limit inflammatory cytokine expression. Moreover, the Examiner contended that Shidoji discloses

that acyclic polyprenyl compounds are activators of PPAR. The Examiner contended that in view of such disclosure there is a reasonable expectation of success of using the acyclic polyprenyl compounds of Shidoji with the disclosure of Marx to treat atherosclerosis and Applicant's recited subject matter would be at hand.

Still further, the Examiner's Answer contends (with emphasis added), on page 6, that:

> Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings of Marx with Shidoji with a reasonable expectation for success in arriving at a method of treating arteriosclerosis by administering a polyprenylcarboxylic acid such as THA. **Marx teaches that PPAR activation results in significant reduction in proinflammatory cytokines. Moreover, Tx-AA is characterized by smooth muscle cell proliferation, which is believed to be driven by cytokine and cytokine-induced growth factors.** PPAR activation may oppose this response as the anti-inflammatory effects of PPAR activation on T lymphocytes contribute to decreased Tx-AA in patients. Although Marx fails to teach administering THA to elicit a PPAR response and treat arteriosclerosis, any ordinary person would have been capable of arriving at such. Shidoji teaches that THA is an excellent PPAR activator and can be administered orally with other pharmaceutical additives. Thus, an ordinary person would be motivated to select and administer THA on subjects with arteriosclerosis with a reasonable expectation in treating the said condition.

Thus, the rejection is basing a statement of expected results on Marx's teachings that PPAR activation results in significant reduction in proinflammatory cytokines. In fact, such assertions are repeated at page 9 and the bottom of page 10 of the Examiner's Answer, with the rejection being supported by asserting of reducing expression of inflammatory cytokines.

However, as shown in the Declaration Under 37 C.F.R. 1.132 of Naoto ISHIBASHI (hereinafter "Declaration") submitted herewith, NIK-333 does not have inhibitory action against the release of each of the cytokines tested in the Experiments, even at 10 μmol/L. Thus, it is concluded in the Declaration that NIK-333 does not have a direct suppressing action against the release of the cytokines in the Experiments.

Therefore, as NIK-333 does not have a direct suppressing action against the release of the cytokines in the Experiments, for this additional reason, it would not have been obvious for one

having ordinary skill to use NIK-333 in Marx. **This is especially the situation in that Marx teaches that the activator of PPAR exhibits anti-arteriosclerosis action via suppression of inflammatory cytokines.** In contrast, the experimental results provided in the Declaration show that the action of NIK-333 against arteriosclerosis is not obtained via suppression of inflammatory cytokines. In Marx, significant suppression of cytokines was found at 100 μM or 250 μM, and suppression of cytokines was also found as low as 10 μM. Whilst, in Shidoji, NIK-333 and WY14643 are taught to achieve almost the same level of activation of PPAR-α, but as shown in the Declaration, NIK-333 has no suppressing action against production of cytokines at 10 μM. Accordingly, it is reasonably understood, and in contrast to the assertions in the rejection, that not all PPAR activators as asserted in the rejection, including NIK-333, as disclosed by Shidoji are applicable to Marx.

Further, Applicant notes that PPAR participates in forming atherosclerosis, whilst KLF5 participates in forming arterial sclerosis due to physical injury of blood vessel after percutaneous transluminal coronary angioplasty (PTCA) and the like. The mode of forming arterial sclerosis by physical injury is fully distinguishable from that of atherosclerosis involving participation of inflammatory cytokines.

Still further, the Examiner's Answer improperly includes the following assertions without the inclusion of any documentary evidence to support the assertions. In particular, the Examiner's Answer, at page 10, includes the following naked asserted:

> First, it's common knowledge that arteriosclerosis is associated with hyperlipidemia and so a population with hyperlipidemia would overlap with a population having arteriosclerosis.
>
> Second, a PPAR activator is a PPAR activator.

With regard to the above, Applicants initially note that as shown by the Declaration, the Examiner's assertion that "a PPAR activator is a PPAR activator" is an overly broad generalization that is not applicable to the present situation. This is especially the case when the activity of NIK-333 is shown in the Declaration to be different than asserted in the rejection.

Moreover, the assertion of common knowledge is without any appropriate basis including any supporting documentary basis. If this assertion of common knowledge is maintained, the Examiner is specifically requested **to provide documentary evidence to support the Examiner's conclusion that arteriosclerosis is associated with hyperlipidemia and so a population with hyperlipidemia would overlap with a population having arteriosclerosis.**

Thus, Applicant submits that there is motivation for one having ordinary skill in the art to combine the disparate disclosures of Marx and Shidoji for at least the reasons set forth above. However, even if for the sake of argument a *prima facie* case of obviousness has been established, which is not the situation, Applicant's claimed subject matter provides unexpected advantages. As shown below, (2E,4E,6E,10E)-3,7,11,15-tetramethyl-2,4,6,10,14-hexadecapentaenoic acid (NIK-333), as recited in Applicant's claims provides advantageous effects as shown with respect to ATRA (all-trans retinoic acid) in view of the experimental results in Example 5 of Applicant's specification for KLF5 inhibition and Example 3-2 for vascular remodeling.

As can be understood from the experimental results of Example 5, at page 11 of Applicant's specification and as illustrated in Fig. 5, NIK-333 provides more potent inhibitory action than ATRA (which was used as a comparative retinoid) against the proliferation of the tested 3T3-KLF5 cells in which KLF5 were stably expressed. In this regard, KLF5 has the action of stimulating proliferation of cells (see, for example, Miyamoto et al., Molecular and

Cellular Biology, Vol. 23, No. 23, Dec. 2003, pp. 8528-8541, such as in the abstract thereof, at lines 4 and 5). In contrast, prior to Applicant's invention, it was known in the field of art that the pharmacological action of ATRA via the retinoid receptor is more potent than NIK-333 (see, Tsurumi et al., International Journal of Hematology, 59, pp. 9-15, 1993 wherein E5166 corresponds to NIK-333). Therefore, the experimental results of Example 5 in Applicant's specification as originally filed establish unexpected results of Applicant's recited (2E,4E,6E,10E)-3,7,11,15-tetramethyl-2,4,6,10,14-hexadecapentaenoic acid. Accordingly, one having ordinary skill in the art would not have expected the results as illustrated in Applicant's originally filed application.

Further, the action of NIK-333 against vascular remodeling was revealed to be more potent than ATRA in Example 3-2 of Applicant's specification by using the mouse cuff-induced injury model, as see pages 9 and 10, and Table 2 of Applicant's specification. Accordingly, one of ordinary skill in the art would not have been able to expect the superior action of NIK-333 than ATRA.

Thus, any combination of the prior art, even if for the sake of argument, the disclosures were combinable, would not arrive at Applicant's independent claim 24 that is directed to a method of treatment for arteriosclerosis, comprising administering to a mammal in need of treatment a medicament comprising (2E,4E,6E,10E)-3,7,11,15-tetramethyl-2,4,6,10,14-hexadecapentaenoic acid as an active ingredient such that activation of a transcription factor KLF5 is inhibited and/or such that vascular remodeling is inhibited.

Moreover, any combination of the prior art, even if for the sake of argument, the disclosures were combinable, would not arrive at Applicant's independent claim 33 that is directed to a method of inhibiting activation of a transcription factor KLF5, comprising

contacting one or more cells which express KLF5 with a composition comprising (2E,4E,6E,10E)-3,7,11,15-tetramethyl-2,4,6,10,14-hexadecapentaenoic acid as an active ingredient such that activation of KLF5 is inhibited.

Yet further, any combination of the prior art, even if for the sake of argument, the disclosures were combinable, would not arrive at Applicant's independent claim 37 that is directed to a method of inhibiting vascular remodeling, comprising administering to a mammal a composition comprising (2E,4E,6E,10E)-3,7,11,15-tetramethyl-2,4,6,10,14-hexadecapentaenoic acid as an active ingredient such that vascular remodeling is inhibited.

Still further, the dependent claims further patentably define the subject matter recited in the independent claim from which they depend. Accordingly, the dependent claims are patentable for at least the reasons set forth above, and for the further features recited therein.

Accordingly, the rejection is without appropriate basis and should be withdrawn.

CONCLUSION

For the reasons discussed above, it is respectfully submitted that the rejections be withdrawn.

Favorable consideration with early allowance of all of the pending claims is most earnestly requested.

If there are any questions regarding the application in general, or the remarks set forth herein, a telephone call to the undersigned would be appreciated since this should expedite the prosecution of the application.

Respectfully submitted,
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